DETAILED ACTION

1. The amendment filed August 2, 2010, is acknowledged and has been entered. Claims 1, 5, 6, 32, 33, 38 and 39 have been amended. Claims 4 and 21 have been canceled.

2. The specification amendment and sequence listing filed February 25, 2011, are acknowledged and have been entered.

3. The election with traverse filed January 12, 2011, is acknowledged and has been entered. Applicant has argued that STn refers to sialyl Tn which is a carbohydrate epitope and this is found persuasive so the species carbohydrate epitope has been rejoined with the elected STn epitope. Furthermore, as claim 1 has been amended to recite a MUC1 epitope and claims 5 and 6 now recite that the immunogenic further comprises carbohydrate epitope or STn, Groups II and III have now been rejoined with the elected Group I as necessitated by this amendment.

4. Claims 1, 2, 5-20, 22-33 and 38-47 are pending. Claims 11, 12, 15, 16, 20, 28, 32, 33, 38-40, 42-44 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention or non-elected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed December 10, 2009.

5. Claims 1, 2, 5-10, 13, 14, 17-19, 22-27, 29-31, 41, 45 and 46 are under examination. The elected species of anti-estrogenic agent administered in the claimed methods that is under consideration is tamoxifen.

Grounds of Objection and Rejection Withdrawn

6. Applicant's amendment and/or arguments filed August 2, 2010, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action. Notably, the prior art references previously cited do not teach administering an immunogen comprising a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and a liposome as set forth in amended claim 1 so the previous prior art rejections have been rendered moot by the amendment.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 2, 5, 10, 13, 14, 17-19, 22, 27, 29-31, 41, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilewski et al (Clin. Can. Res., 6:1693-1701, 2000, of record) in view of Budzynski et al (WO 02/076485 A2 in view of Maurer et al (Exp. Opin. Biol. Ther., 1(6):923-947, 2001) and in view of Buzdar et al (Clin. Can. Res., 4:527-534, 1998, of record).

The claims are herein drawn to method comprising administering to a subject with breast cancer or metastatic breast cancer a first amount of anti-estrogenic steroid agent, effective to reduce the level or activity of at least one estrogenic steroid in the subject, and a second amount of an immunological agent, effective to contribute to the development of a protective immune response to said breast cancer, where said first and second amounts are, at least in combination, therapeutically effective against at least some breast cancers, where said immunological agent comprises at least one immunogen, where said immunogen comprises (i) an immunogen comprises a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and (ii) a liposome (see claims 1 and 31). Claim 2 recites that the agents are administered concurrently. In this case, the specification does not explicitly define concurrent administration as simultaneous administration, so concurrent administration is being broadly, but reasonably interpreted to include administration of the two agents separately to the same breast cancer patient in conjunction or in combination with one another. For example, Merriam-Webster's Online Dictionary. Definition of concurrent, 2011 [online], [retrieved on 11/7/2011]. Retrieved from the internet: <URL: http://www.merriam-webster.com/dictionary/concurrent> (copyright © 2011 by Merriam-Webster, Inc.), defines the term “concurrent” as:

1: operating or occurring at the same time

2 a : running parallel **b : CONVERGENT**; *specifically* **:** meeting or intersecting in a point

3 : acting in conjunction

4: exercised over the same matter or area by two different authorities <*concurrent* jurisdiction>

Claim 5 further recites that the immunogen comprises a carbohydrate epitope. As drawn to the elected species, claims 10, 13, 14, 27, 29, 30, 41, 45 and 46 are further drawn to the anti-estrogenic agent being the Selective Estrogen Receptor Modulator (SERM) tamoxifen. Claims 17-19 are further drawn to the methods further comprising administering progesterone or an anti-progestin to the subject. Claim 22 recites further administering a chemotherapeutic agent.

Gilewski et al teach methods of treating metastatic breast cancer patients comprising administering to said patients a hormonal agent known to treat breast cancer and a MUC1 immunogen to induce an immune response to the immunogen and that these agents are administered to subjects in conjugation with each other. (see entire document, e.g., pages 1693, right column and 1694, right column). Gilewski et al further teach chemotherapy as a treatment for breast cancer (see page 1694, right column).

Gilewski et al does not expressly teach an MUC1 immunogen comprising a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and a carbohydrate epitope and (ii) a liposome. Gilewski et al also does not expressly teach administering the hormonal therapies tamoxifen, progesterone or an anti-progestin to breast cancer subjects.

These deficiencies are made up for in the teachings of Budzynski et al, Maurer et al and Buzdar et al.

Budzynski et al teach an MUC1 immunogen comprising a MUC1 epitope comprising the amino acid sequence of SEQ ID NO: 1 and a carbohydrate epitope and (ii) a liposome (see entire document, e.g., page 21 and alignment below). Budzynski et al further teach that attaching lipids to peptides leads to the

induction of strong T-cell proliferation, CTL responses and antibody responses (see page 2).

```
RESULT 7
AAE33943
ID   AAE33943 standard; peptide; 20 AA.
XX
AC   AAE33943;
XX
DT   02-MAY-2003  (first entry)
XX
DE   MUC 1 peptide #5.
XX
KW   Liposome; vaccine; immune response; MUC 1 lipopeptide;
immunomodulator;
KW   T cell proliferation; antibody production.
XX
OS   Unidentified.
XX
PN   WO200276485-A2.
XX
PD   03-OCT-2002.
XX
PF   27-MAR-2002; 2002WO-IB002188.
XX
PR   27-MAR-2001; 2001US-0278698P.
XX
PA   (BUDZ/) BUDZYNSKI W A.
XX
PI   Budzynski WA,  Budzynski RR,  Koganty MJ,  Longenecker MB;
XX
DR   WPI; 2003-046750/04.
XX
PT   New liposome vaccines comprising at least one monolipopeptide and
at
PT   least one dilipopeptide, useful for modulating the immune response
in
PT   vivo, particularly humoral and cellular immune responses.
XX
PS   Disclosure; Page 21; 51pp; English.
XX
CC   The present invention relates to liposomal compositions comprising
at
CC   least one liposome that comprises at least one monolipopeptide and
at
CC   least one dilipopeptide derived from a protein associated with a
disease
CC   selected from the group consisting of tuberculosis, malaria,
cancer and
CC   hepatitis B. The monolipopeptide or dilipopeptide is designed from
MUC 1
CC   protein. The composition is useful as a vaccine for modulating the
immune
CC   response to the peptide in vivo, particularly humoral and cellular
immune
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CC   responses where the relative amounts of monolipopeptide and
dilipopeptide
CC   modulate the relative intensities of T cell proliferation and
antibody
CC   production. The present sequence is MUC 1 peptide
XX
SQ   Sequence 20 AA;

  Query Match             100.0%;  Score 109;  DB 1;  Length 20;
  Best Local Similarity   100.0%;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 GVTSAPDTRPAPGSTAPPAH 20
              ||||||||||||||||||||
Db          1 GVTSAPDTRPAPGSTAPPAH 20
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Maurer et al teach that encapsulating peptides in liposomes acts as an a immunological adjuvant that stimulates both a humoral and cellular immune response (see entire document, e.g., page 934).

Buzdar et al teach that administering tamoxifen, progesterone, an anti-progestin and/or cytotoxic chemotherapy are art recognized treatments for breast cancer (see entire document, e.g., pages 527 and 532).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat breast cancer by administering a MUC1 immunogen comprising a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and a carbohydrate epitope and (ii) a liposome in conjunction with tamoxifen and progesterone, an anti-progestin and/or cytotoxic chemotherapy to metastatic breast cancer subjects.

Notably, based on the teachings of Budzynski et al and Maurer et al relating to increased T-cell proliferation, CTL and antibody responses using liposome encapsulated and lipid-conjugated peptides, one of skill in the art would have been motivated to use the MUC1 immunogens of Budzynski et al that comprise a MUC1 epitope comprising the amino acid sequence of SEQ ID NO: 1 and a carbohydrate epitope and (ii) a liposome to treat breast cancer in order to increase the immune response in patients. In this case, Gilewski et al teach that their immunogen produces a significant antibody response, but no evidence of T

cell activation (see page 1698, left column), so one of skill in the art would have been further motivated to use the immunogens of Budzynski et al to generate increased T-cell proliferation and CTL responses. Furthermore, as Gilewski et al teach treating breast cancer with chemotherapy and hormonal agents and as Buzdar et al teach that administering tamoxifen, progesterone, an anti-progestin and/or cytotoxic chemotherapy are art recognized treatments for breast cancer, one of skill in the art would immediately recognize that tamoxifen, progesterone, an anti-progestin and cytotoxic chemotherapy are additional treatments effective in breast cancer patients so one of skill in the art would have been motivated to also administer tamoxifen and one or more of the other agents to breast cancer patients along with the MUC1 immunogen compositions of Budzynski et al to effectively treat the subject's breast cancer. One of skill in the art would have been further motivated to also administer these agents because Gilewski et al evidence that hormonal agents were being administered to patients that also received administration of a MUC1 immunogen and that these patients have also received chemotherapy. Accordingly, one of skill in the art would not have considered it inventive to predictably add administration of these art recognized agents to treat a subject's breast cancer since administration of these agents to breast cancer patients was taught by the art.

Finally, one of skill in the art also would have reasonably expected success in treating at least some breast cancers as claimed by administering the MUC1 immunogen compositions of Budzynski et al in combination with tamoxifen, progesterone, an anti-progestin and cytotoxic chemotherapy because the art taught administration of MUC1 immunogen compositions, tamoxifen, progesterone, anti-progestins and cytotoxic chemotherapy to treat breast cancer as evidenced by the references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilewski et al (Clin. Can. Res., 6:1693-1701, 2000, of record) in view of Budzynski et al (WO 02/076485 A2) in view of Maurer et al (Exp. Opin. Biol. Ther., 1(6):923-947, 2001) and in view of Buzdar et al (Clin. Can. Res., 4:527-534, 1998, of record), as applied to claims 1, 2, 5, 10, 13, 14, 17-19, 22, 27, 29-31, 41, 45 and 46 above and further in view of Holmberg et al (Exp. Opin. Biol. Ther., 1(5):881-891, 2001).

Claims 6-9 are further drawn to is further drawn to the immunogen comprising an STN-KLH conjugate (see claims 6 and 7), wherein the conjugate is an aggregated conjugate (see claim 8) and wherein the conjugate has a NANA content of about 7% (see claim 9).

Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al teach and suggest what is set forth in the above 103 (a) rejection.

However, Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al do not expressly teach or suggest an immunogen comprising an STn-KLH conjugate, wherein the conjugate is an aggregated conjugate and wherein the conjugate has a NANA content of about 7%

These deficiencies are made up for in the teachings of Holmberg et al.

Holmberg et al teach that cancer MUC1 antigen contains an STn carbohydrate and making a THERATOPE STn-KLH conjugate that comprises NANA and administering said conjugate to metastatic breast cancer patients in a Phase III clinical trial (see entire document, e.g., abstract, page 881 and Figure 1). While Holmberg et al do not disclose the properties of the STn-KLH conjugate that they administer, as set forth in the instant specification the THERATOPE STn-KLH conjugate used in Phase III clinical trials is an aggregated conjugate with a NANA content of about 7% (see pages 4 and 5). Accordingly, absent a showing otherwise, the THERATOPE STn-KLH conjugate of Holmberg et al necessarily is an aggregated conjugate with a NANA content of about 7%. In this case, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to

establish that the product of the prior art possesses the same material, structural, and functional characteristics as Applicant's product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the product administered in the methods to which the claims are directed is different than that taught by the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and Ex parte Gray, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat breast cancer by administering a MUC1 immunogen comprising a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and an STn-carbohydrate epitope conjugated to KLH and (ii) a liposome in conjunction with tamoxifen and progesterone, an anti-progestin and/or cytotoxic chemotherapy to metastatic breast cancer subjects.

Notably, based on the teachings of Holmberg et al that the THERATOPE STn-KLH conjugate is in Phase III clinical trials for breast cancer, one of skill in the art would have been motivated to add the THERATOPE STn-KLH conjugate to the MUC1 peptide of Budzynski et al and the other claimed breast cancer treatments in order to more effectively treat the breast cancer because all the treatments were known in the art. Furthermore, Gilewski et al suggest adding additional antigenic epitopes such as glycosylated MUC1 peptides to their treatments (see page 1699, left column), so one of skill in the art would have been motivated to add the STn-carbohydrate epitope conjugated to KLH to the peptides of Budzynski et al. Finally, one of skill in the art also would have reasonably expected success in treating at least some breast cancers as claimed because the art taught administration of MUC1 immunogen compositions, STN-KLH compositions, tamoxifen, progesterone, anti-progestins and cytotoxic chemotherapy to treat breast cancer as evidenced by the references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilewski et al (Clin. Can. Res., 6:1693-1701, 2000, of record) in view of Budzynski et al (WO 02/076485 A2) in view of Maurer et al (Exp. Opin. Biol. Ther., 1(6):923-947, 2001) and in view of Buzdar et al (Clin. Can. Res., 4:527-534, 1998, of record), as applied to claims 1, 2, 5, 10, 13, 14, 17-19, 22, 27, 29-31, 41, 45 and 46 above and further in view of Koganty et al (WO 03/015796 A1).

Claims 6-9 are decribed supra.

Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al teach and suggest what is set forth in the above 103 (a) rejection.

However, Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al do not expressly teach or suggest an immunogen comprising an STN-KLH conjugate, wherein the conjugate is an aggregated conjugate and wherein the conjugate has a NANA content of about 7%.

These deficiencies are made up for in the teachings of Koganty et al.

Koganty et al teach that cancer MUC1 antigen contains an STn carbohydrate and making a THERATOPE STn-KLH aggregated conjugate that comprises NANA at about 7% and administering said conjugate to patients in clinical trials (see entire document, e.g., pages 1-6).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat breast cancer by administering a MUC1 immunogen comprising a MUC1 epitope having one to eight effective tandem repeats of SEQ ID NO: 1 and an aggregated STn-carbohydrate epitope conjugated to KLH that comprises NANA at about 7% and (ii) a liposome in conjunction with tamoxifen and progesterone, an anti-progestin and/or cytotoxic chemotherapy to metastatic breast cancer subjects.

Notably, based on the teachings of Koganty et al that the STn-KLH conjugate is in clinical trials and is another cancer epitope on the MUC1 breast cancer antigen, one of skill in the art would have been motivated to add the STn-KLH conjugate of Koganty et al to the MUC1 peptide of Budzynski et al and the other claimed breast cancer treatments in order to more effectively treat the breast cancer. Furthermore, Gilewski et al suggest adding additional antigenic epitopes such as glycosylated MUC1 peptides to their treatments (see page 1699, left column), so one of skill in the art would have been motivated to add the MUC1 STn-carbohydrate epitope conjugated to KLH to the peptides of Budzynski et al. Finally, one of skill in the art also would have reasonably expected success in treating at least some breast cancers as claimed because the art taught administration of MUC1 immunogen compositions, STN-KLH compositions, tamoxifen, progesterone, anti-progestins and cytotoxic chemotherapy as evidenced by the references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claims 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilewski et al (Clin. Can. Res., 6:1693-1701, 2000, of record) in view of Budzynski et al (WO 02/076485 A2) in view of Maurer et al (Exp. Opin. Biol. Ther., 1(6):923-947, 2001) and in view of Buzdar et al (Clin. Can. Res., 4:527-534, 1998, of record), as applied to claims 1, 2, 5, 10, 13, 14, 17-19, 22, 27, 29-31, 41, 45 and 46 above and further in view of Nabholtz et al (Onc., 6(S3)5-12, 2001, of record).

Claim 23-26 are further drawn to administering the chemotherapeutic agent doxorubicin (see claim 24) or paclitaxel (see claim 26) to the subject.

Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al teach and suggest what is set forth in the above 103 (a) rejection.

However, Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al do not expressly teach or suggest administering doxorubicin or paclitaxel to breast cancer subjects. This deficiency is made up for in the teachings of Nabholtz et al.

Nabholtz et al teach that teach that administering doxorubicin or paclitaxel as chemotherapy to breast cancer subjects was known in the art. (see entire document, e.g., abstract).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer doxorubicin and/or paclitaxel as chemotherapy along with the treatments suggested by Gilewski et al, Budzynski et al, Maurer et al and Buzdar et al

Notably, based on the teachings of Nabholtz et al one of skill in the art would immediately recognize that doxorubicin and/or paclitaxel are chemotherapeutic agents effective in breast cancer patients so one of skill in the art would have been motivated to administer one or more of these agents to breast cancer patients along with the other agents taught in the art to effectively treat the subject's breast cancer. Furthermore, as evidenced by Gilewski et al and Buzdar et al chemotherapy is often administered to breast cancer patients who have also received other agents such as those instantly claimed. Accordingly, one of skill in the art would not have considered it inventive to predictably add administration of doxorubicin and/or paclitaxel to treat a subject's breast cancer since administration of these agents to breast cancer patients was taught by the art. Furthermore, because administration of these agents to breast cancer patients was taught by the art, one of skill in the art clearly would have had a reasonable expectation of success in administering such agents to breast cancer patients, in view of these references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Thursday 6:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/bd/
Examiner, Art Unit 1643
November 3, 2011

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1642